B24

blooded animal an effective amount of a compound according to claim 7 or 8, wherein said disease or medical condition is a tumor selected from melanoma, seminoma, teratocarcinoma, neuroblastoma and glioma.

REMARKS

I. Amendments to the Specification

In response to the Examiner's comments, and in order to expedite prosecution, Applicants have made several amendments to the specification. Most notably, Applicants have amended the terms L in Formula I, n (as used in describing certain embodiments of linking moiety L), A (as used in the term "Formula A"), n (as used in Formula A), and Y in the preferred subclass of Formula A to refer to the terms G, w, B, e, and Y' respectively. Applicants have also corrected several typographical errors in the text of the specification. No new matter has been added as a result of these amendments.

II. Status of the Claims

Claims 7-9 and 13 have been amended and remain pending. Claims 18-22 have been added and claims 1, 3, 10-12, and 14-17 have been cancelled.

Applicants wish to thank the Examiner for the Interview held in March, 2002. In view of our discussions, Applicants have amended, cancelled, and added claims accordingly. For the reasons provided below, Applicants submit that all pending claims are now in condition for allowance.

A. Claims 18-22

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

In the Interview, the Examiner indicated that claim 18 was acceptable for allowance, and, further, that claims 19-22 would be acceptable for allowance provided that the Applicants could establish an art recognized nexus between the inhibition of farnesylation and the treatment of the claimed tumor.

MPEP §2164.02 states that an *in vitro* or *in vivo* model example in the specification, in effect constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention. Furthermore, "if the art is such that a particular model is recognized as correlating to a specific condition then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate." (MPEP §2164.02).

In this case, the claimed disease states susceptible to these treatments are each specifically disclosed in the specification, *e.g.*, on pages 1 and 28. Moreover, prior art publications such as Mariano Barbacid, "ras Genes," Ann. Rev. Biochem., 56:779-827 (1987), demonstrate that ras oncogenes are associated with the claimed types of carcinomas and thus, would be treatable through the claimed methods and compounds which act to inhibit farnesylation.

Likewise, the specification also provides, on pages 41-42, data regarding the *in vitro* inhibitory activity of the various disclosed compounds against the farnesyl protein transferase enzyme, including specified efficacious concentrations. Such activity can be correlated to *in vivo* treatments of the claimed disease states based on knowledge in the art. For example, U.S. Patent No. 5,141,851 at col. 11, lines 47-57 discloses "it is believed that by inhibiting the farnesyl transferase enzyme, one will be enabled to treat various aspects of cancers, such as ras-related cancers." Furthermore, it is also known

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

in the art that such treatments "may be useful by themselves or in conjunction with other cancer therapies." (*Id.*)

The Federal Circuit has stated and reiterated that therapeutic sufficiency under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to market in the United Sates. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). MPEP § 2107. Thus, the data provided in the specification adequately supports and correlates to the claimed methods of treatment.

B. Claims 7-9 and 13

The Examiner also indicated during the Interview that the remaining pending claims, specifically claims 7-9 and 13, would be allowable with the amendments provided herein. Accordingly, Applicants believe that these claims are allowable in view of the Examiner's outstanding rejections presented in the Office Action dated November 11, 2001.

III. Markush Rejection

In the Office Action, the Examiner asserts that claims 7-9 and 13 contain improper Markush groups. Specifically, the Examiner states that the term L in formula I and n in formula A are duplicative of other terms in the specification and thus, have different definitions, rendering the claims improper (Paper No. 8, page 3). As discussed during the recent interview, Applicants have amended claim 7 and the specification to address the Examiner's concerns. Applicants respectfully request withdrawal of this rejection.

IV. Rejection Under 35 U.S.C. §112, First Paragraph

A. "Prodrugs"

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

The Examiner has rejected claims 9 and 13 under 35 U.S.C. §112, first paragraph, asserting that the scope of the term "prodrug" is not adequately enabled. As discussed with the Examiner during the recent interview, the pending claims, as amended, no longer use the term "prodrug." On this basis, withdrawal of this rejection is respectfully requested.

B. "Inhibition of Farnesylation of Mutant Ras Gene"

The Examiner has rejected claims 9 and 13 under 35 U.S.C. §112, first paragraph, asserting that the inhibition of farnesylation of mutant ras gene is not enabled. As discussed with the Examiner in the recent interview, neither claim 9 nor claim 13, as amended, contains such a limitation. Thus, Applicants respectfully request that the Examiner withdraw this rejection.

V. Rejections Under 35 U.S.C. §112, Second Paragraph

A. The Examiner has rejected claims 9 and 13 as vague and indefinite and that it is not known how the -S-S- dimer can be made when the S atom of the pyrrole is substituted with a hydrogen atom. As discussed with the Examiner during the recent interview, claims 9 and 13, as amended, are no longer directed to the -S-S dimer referenced by the Examiner in this rejection. Thus, Applicants respectfully request that the Examiner withdraw this rejection.

B. The Examiner has rejected claim 7 for being vague and indefinite in that there is an "additional definition for the variable n." As discussed, Applicants have amended each "n" term to an "e" term, as the term appears in claim 7 and the specification. Likewise, given that amended claims 9 and 13 now depend from claim 7, these

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

amendments also address the same rejection of those claims. Therefore, withdrawal of this ground of rejection is respectfully requested.

C. The Examiner has also rejected claim 13 for being vague and indefinite for an unmatched parenthesis, present in claim 1, from which it depended. Applicants have amended claim 13, such it no longer depends from cancelled claim 1, which contained the referenced language. Therefore, withdrawal of this ground of rejection is respectfully requested.

VI. Rejection Under 35 U.S.C. §103(a)

The Examiner has rejected claims 7-9 and 13 under 35 U.S.C. §103(a) as being obvious over Leftheris, U.S. Patent No. 5,929,077. Applicants respectfully traverse this rejection.

The subject matter of the pending claims, as amended, are all entitled to the earliest claimed priority dated of August 17, 1996. The Leftheris patent has a later provisional filing date of November 8, 1996 and, thus, does not represent prior art under 35 U.S.C. § 102. Accordingly, Applicants respectfully request withdrawal of this rejection.

Furthermore, as discussed in the March, 2002 Interview with the Examiner, Applicants' claimed invention is directed to 3-mercaptopyrrolidine compounds. Leftheris et al., on the other hand, teach away from the claimed compounds, instead disclosing 4-mecaptopyrrolidine compounds. Rather, the cited reference discloses a specifically substituted a mercapto moiety in the 3-position only for the cyclopentyl system, which is a non-pyrrolidine system. Therefore, in accordance with our discussions with the

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Examiner, Applicants maintain that the Leftheris reference does not teach or suggest the claimed invention.

VII. Conclusion

The Applicants respectfully request that this Amendment under 37 C.F.R. § 1.115 be entered by the Examiner, placing claims 1-22 in condition for allowance. As discussed, Applicants submit that that the proposed additional claims 18-22, having already been discussed with the Examiner in a recent interview, do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner. Likewise, Applicants have overcome all outstanding rejections of the remaining claims. Therefore, this Amendment should allow for immediate action by the Examiner.

Moreover, Applicants submit that the entry of the amendment would place the application in better form for appeal, should the Examiner dispute the patentability of the pending claims.

In view of the foregoing remarks and recent discussions with the Examiner, Applicants request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: October 15, 2002

By: Walter W. Brown
Walter W. Brown
Reg. No. 47,457

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

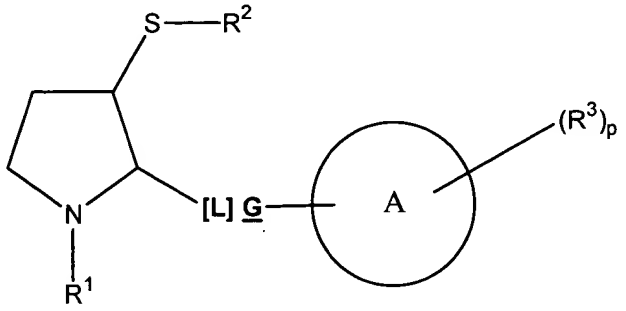
APPENDIX TO AMENDMENT OF FEBRUARY 15 2002

Version with Markings to Show Changes Made

Amendments to the Specification

First paragraph on page 2, beginning at line 6 and ending at page 4, line 9:

According to one aspect of the present invention there is provided an inhibitor of ras farnesylation of Formula I



wherein:

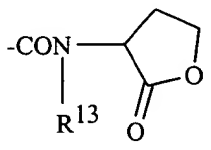
R^{1} is selected from H; -C_{1-4}alkyl; -CO-C_{1-4}alkyl; -CO-O-C_{1-4}alkyl; -CO-O-C_{2-4}alkenyl; -C_{1-4}alkylene-$CONR^4R^5$ (wherein R^4 and R^5 are independently selected from H and C_{1-4}alkyl); -C_{1-4}alkylene-$COOR^6$ (wherein R^6 is selected from H and C_{1-4}alkyl); -C_{1-3}alkylene-Ph and -CO-O$(CH_2)_n$Ph wherein the phenyl groups in -C_{1-3}alkylene-Ph and -CO-O$(CH_2)_n$Ph are optionally substituted by R^a and/or R^b and R^a and R^b are independently selected from C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkanoylamino, nitro, cyano, carboxy, carbamoyl, C_{1-4}alkoxycarbonyl, thiol, C_{1-4}alkylsulfanyl, C_{1-4}alkylsulfinyl,C_{1-4}alkylsulfonyl and sulfonamido; and n=0-4;

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

R^2 is selected from H; -C_{1-4}alkyl; -COC_{1-4}alkyl; and -$COOC_{1-4}$alkyl; and -C_{1-3}alkylene-Ph optionally substituted on the phenyl ring by R^a and/or R^b;

R^3 is selected from H; OH; CN; CF_3; NO_2; -C_{1-4} alkyl; -C_{1-4}alkylene-R^7; -C_{2-4}alkenylene-R^7; -C_{2-4}alkynylene-R^7; R^7; OR^7 (where R^7 is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing [upto]up to 5 heteroatoms selected from [O,N]O, N and S and any aryl ring in R^7 is optionally substituted by R^a and/or R^b); C_{2-4}alkenyl; halogen; -$(CH_2)_{[n]y}COOR^8$ (where [n^1] y = 0-3 and R^8 represents H, C_{1-4}alkyl, or C_{2-4}alkenyl)[;-]; -$CONR^9R^{10}$ (where R^9 and R^{10} independently represent H, C_{1-4}alkyl, C_{2-4}alkenyl, -O-C_{1-4}alkyl, -O-C_{2-4}alkenyl or -C_{1-3}alkylenePh (wherein Ph is optionally substituted by R^a and R^b as hereinabove defined);-$CON(R^{11})OR^{12}$ (where R^{11} and R^{12} independently represent H, C_{1-4}alkyl or C_{2-4}alkenyl);

a group of the Formula II: -$CONR^{13}$-CR^{13a} R^{14}-$COOR^{17}$, (where R^{13} and R^{13a} are independently H or C_{1-4}alkyl, R^{17} is H or C_{1-6}alkyl, R^{14} is selected from the side chain of a lipophilic amino acid, carbamoylC_{1-4}alkyl, N-(monoC_{1-4}alkyl)carbamoylC_{1-4}alkyl and N-(diC_{1-4}alkyl)carbamoylC_{1-4}alkyl[]], the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula:



;

C_{1-4}alkyl monosubstituted on carbon with =N-OH;

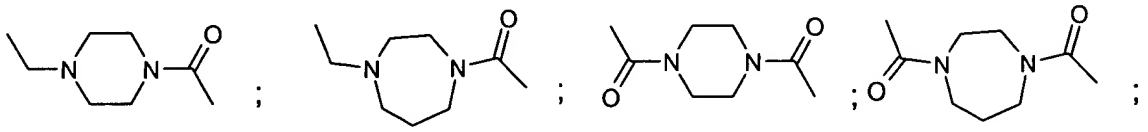
a group of Formula -X-R^{15} (where X is selected from O, CO, CH_2, S, SO, SO_2 and R^{15} is selected from C_{1-6}alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

heteroaryl ring containing [upto]up to 5 heteroatoms selected from [O,N]O, N and S and any aryl ring in R^{15} is optionally substituted by R^a and/or R^b;

p is 0-3 in which R^3 values can be the same or different;

[L]G is a linking moiety selected from the following groups written from left to right in Formula I:



(wherein the piperazine and perhydro-1,4-diazepine rings are optionally substituted); $-CO-NR^{16}-$; $-CH_2-NR^{16}-$; $-CH_2S-$; $-CH_2O-$; $-CH_2-CHR^{16}$; $-CH=CR^{16}-$; $-CH_2NR^{16}-T-$; $-CH_2NR^{16}-SO_2-$; $-CH_2-NR^{16}-CO-T^1-$; $-CO-NR^{16}-T-$; $-CH_2S-T-$; $-CH_2O-T-$ (where R^{16} is selected from H, C_{1-4}alkyl, C_{1-4}alkylene-Z, $-CO-C_{1-4}$alkylene-Z, $-CO-C_{1-6}$alkyl, -COZ, Z and Z is selected from $-O-C_{1-4}$alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing [upto]up to 5 heteroatoms selected from O, N and S and any aryl ring in R^{16} is optionally substituted by R^a and/or R^b as hereinabove defined; where, T represents $-(CH_2)m-$ where m is 1-4 and T is optionally monosubstituted with any value of R^{16} other than H; and

where T^1 represents $-(CH_2)m^1-$ wherein m^1 is 0-4 and [T]T^1 is optionally monosubstituted with any value of R^{16} other than H);

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing [upto]up to 5 heteroatoms where the heteroatoms are independently selected from O, N & S;

or a -S-S- dimer thereof when R^2=H; or a N-oxide thereof; or a pharmaceutically acceptable salt, prodrug or solvate thereof.

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

First paragraph on page 4, beginning at line 10 and ending at page 6, line 11:

In another aspect of the invention there is provided an inhibitor of ras farnesylation of Formula I

wherein:

R^1 is selected from H; -C_{1-4}alkyl; -C_{1-3}alkylene-Ph optionally mono or di-substituted on Ph with substituents selected from C_{1-4}alkyl, halogen, OH, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkanoylamino, nitro, cyano, carboxy, carbamoyl, C_{1-4}alkoxycarbonyl, thiol, C_{1-4}alkylsulfanyl, C_{1-4}alkylsulfinyl,C_{1-4}alkylsulfonyl and sulfonamido; -CO-C_{1-4}alkyl; -CO-O-C_{1-4}alkyl; -CO-O-C_{2-4}alkenyl; -CO-O-$(CH_2)_n$Ph optionally substituted on Ph as defined for substitution on Ph in R^1 = -C_{1-3}alkylene-Ph above and n=0-4; -C_{1-4}alkylene-CONR^{4}R^5 where R^4 & R^5 are independently selected from H and C_{1-4}alkyl; and -C_{1-4}alkylene-COOR^6 where R^6 is selected from H, C_{1-4}alkyl;

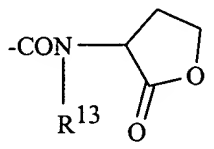
R^2 is selected from H; -C_{1-4}alkyl; -C_{1-3}alkylene-Ph optionally substituted on Ph as defined for substitution on Ph in R^1 = -C_{1-3}alkylene-Ph above; -COC_{1-4}alkyl; and -COOC_{1-4}alkyl;

R^3 is selected from H; OH; CN; CF_3; NO_2; -C_{1-4} alkyl; -C_{1-4}alkylene-R^7 where R^7 is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing [upto]up to 5 heteroatoms selected from [O,N]O, N and S and any aryl ring in R^7 is optionally substituted as defined for substitution on the Ph group in R^1 = -C_{1-3}alkylene-Ph above; R^7; C_{2-4}alkenyl; halogen; -$(CH_2)_{[n]y}$COOR^8 where [n]y= 0-3 and R^8 represents H, C_{1-4}alkyl, or C_{2-4}alkenyl; -CONR^{9}R^{10} where R^9 and R^{10} independently represent H, C_{1-4}alkyl, C_{2-4}alkenyl, -O-C_{1-4}alkyl, -O-C_{2-4}alkenyl, -C_{1-3}alkylenePh

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

optionally substituted as defined for this group for R^1 above[;-]; -$CON(R^{11})OR^{12}$ where R^{11} and R^{12} independently represent H, C_{1-4}alkyl and C_{2-4}alkenyl;

a group of Formula II, -$CONR^{13}$-CHR^{14}-$COOR^{17}$, where R^{13} is H or C_{1-4}alkyl, R^{17} is H or C_{1-6}alkyl, R^{14} is selected from the side chain of a lipophilic amino acid, carbamoylC_{1-4}alkyl, N-(monoC_{1-4}alkyl)carbamoylC_{1-4}alkyl and N-(diC1-4alkyl)carbamoylC_{1-4}alkyl, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula



;

C_{1-4}alkyl monosubstituted on carbon with =N-OH;

a group of Formula -X-R^{15} where X is selected from O, CO, CH_2, S, SO, SO_2 and R^{15} is selected from C_{1-6}alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing [upto]up to 5 heteroatoms selected from [O,N]O, N and S and any aryl ring in R^{15} is optionally substituted as defined for the Ph group in R^1 = -C_{1-3}alkylene-Ph;

p is 0-3 in which R^3 values can be the same or different;

[L]G is a linking moiety selected from the following groups written from left to right in Formula I:

-CO-NR^{16}- where R^{16} is selected from H, C_{1-4}alkyl, C_{1-4}alkylene-Z, -CO-C_{1-4}alkylene-Z, -CO-C_{1-6}alkyl, -COZ, Z and Z is selected from -O-C_{1-4}alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing [upto]up to 5 heteroatoms selected from O, N and S and any aryl ring in R^{16} is optionally substituted as defined for the Ph group in R^1 = -C_{1-3}alkylene-Ph; -CH_2-NR^{18}- where R^{18} represents any value

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

defined for R^{16}; $-CH_2S-$; $-CH_2O-$; $-CH_2-CHR^{19}-$ where R^{19} represents any value defined for R^{16}; $-CH=CR^{20}-$ where R^{20} represents any value defined for R^{16}; $-CH_2NR^{21}$-T- where R^{21} represents any value defined for R^{16}, T represents $-(CH_2)$[n]w- where [n]w is 1-4 and T is optionally monosubstituted with R^{22} where R^{22} represents any value for R^{16} other than H; $-CH_2NR^{23}-SO_2-$ where R^{23} represents any value defined for R^{16} ; $-CH_2-NR^{24}$-CO-T- where R^{24} represents any value defined for R^{16}, T represents $-(CH^2)^{[n]w}-$ where [n]w is 0-4 and T is optionally monosubstituted with R^{29} where R^{29} represents any value for R^{16} other than H; $-CO-NR^{25}$-T- where R^{25} represents any value defined for R^{16}, T represents $-(CH_2)_{[n]w}-$ where [n]w is 1-4 and T is optionally monosubstituted with R^{26} where R^{26} represents any value for R^{16} other than H; $-CH_2S$-T- where T represents $-(CH_2)$[n]w- where [n]w is 1-4 and T is optionally monosubstituted with R^{27} where R^{27} represents any value for R^{16} other than H; $-CH_2O$-T- where T represents $-(CH_2)_n-$ where n is 1-4 and T is optionally monosubstituted with R^{28} where R^{28} represents any value for R^{16} other than H;

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing [upto]up to 5 heteroatoms where the heteroatoms are independently selected from O, N & S;

or a -S-S- dimer thereof when R^2=H; or a N-oxide thereof;

or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof.

Add paragraph beginning page 6, line 26 to page 8, line 9.

Examples of **C_{1-6}alkyl** include methyl, ethyl, propyl, isopropyl, *sec*-butyl, *tert*-butyl and pentyl; examples of **C_{1-4}alkyl** include methyl, ethyl, propyl, isopropyl, *sec*-butyl and

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

tert-butyl; examples of **C_{1-3}alkyl** include methyl, ethyl, propyl and isopropyl; examples of - **C_{1-3}alkylenePh** include benzyl, phenylethyl, phenylpropyl; examples of **C_{1-4}alkoxy** (also called **-O-C_{1-4}alkyl** herein) include methoxy, ethoxy and propoxy; examples of **C_{1-4}alkanoyl** include formyl, acetyl and propionyl; examples of **C_{1-4}alkanoyloxy** include acetyloxy and propionyloxy; examples of **$C_{1=4}$alkylamino** include methylamino, ethylamino, propylamino, isopropylamino, *sec*-butylamino and *tert*-butylamino; examples of **di-(C_{1-4}alkyl)amino** include di-methylamino, di-ethylamino and N-ethyl-N-methylamino; examples of **C_{1-4}alkoxnoylamino** include acetamido and propionylamino; examples of **C_{1-4}alkoxycarbonyl** include methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; examples of **C_{1-4}alkylsulfanyl** include methylsulfanyl, ethylsulfanyl, propylsulfanyl, isopropylsulfanyl, *sec*-butylsulfanyl and *tert*-butylsulfanyl; examples of **C_{1-4}alkylsulfinyl** include methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, *sec*-butylsulfinyl and *tert*-butylsulfinyl; examples of **C_{1-4}alkylsulfonyl** include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, *sec*-butylsulfonyl and *tert*-butylsulfonyl; examples of **-CO-C_{1-4}alkyl** include formyl, acetyl, propionyl, butyryl, and valeryl; examples of **-CO-O-C_{1-4}alkyl** include ethyloxycarbonyl; propyloxycarbonyl and *tert*-butyloxycarbonyl (BOC); examples of **-CO-O-$(CH_2)_y$Ph** where y=0-4 include phenyloxycarbonyl, benzyloxycarbonyl, phenylethyloxycarbonyl and phenylpropyloxycarbonyl; examples of **-C_{1-4}alkylene-CONR^{4}R^5** include carbamoylmethyl, carbamoylethyl, N-methylcarbamoylethyl, N-methyl-N-ethylcarbamoylethyl; examples of **-C_{1-4}alkylene-COOR^6** include caroxymethyl, carboxyethyl, carboxypropyl, propionic acid methyl ester, acetic acid ethyl ester; examples of **C_{2-4}alkenyl** include allyl and vinyl; examples of **-O-C_{2-4}alkenyl** include

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

allylocy and vinyloxy; examples of **lipophilic amino acids** include valine, leucine, isoleucine, methionine, phenylalanine, serine, threonine and tyrosine; examples of **carbomoylC_{1-4}alkyl** include carbomoylmethyl, carbamoylethyl and carbamoylpropyl; examples of **N-(monoC_{1-4}alkyl)carbamoylC_{1-4}alkyl** include N-methylcarbamoylmethyl and N-ethyl-carbamoylethyl; examples of **N-(diC_{1-4}alkyl)carbamoyl-C_{1-4}alkyl** include N,N-dimethylcarbamoylethyl and N-methyl-Nethylcarbamoylethyl; examples of **C_{1-4}alkyl monosubstituted on carbon with =N-OH** include butyraldehyde oxime and propionaldehyde oxime; examples of **hydroxyC_{1-6}alkyl** include hydroxymethyl, hydroxyethyl, hydroxypropyl, 2-hydroxypropyl, 2-(hydroxymethyl)propyl and hydroxypentyl; examples of **C_{1-6}alkoxyC_{1-6}alkyl** include methoxyethyl, ethoxyethyl and methoxybutyl; examples of **C_{1-6}alkylcarbonyl** include methylcarbonyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, *sec*-butylcarbonyl, *tert*-butylcarbonyl and pentylcarbonyl; examples of **hydroxyC_{1-6}alkylcarbonyl** include hydroxyacetyl, hydroxypropionyl, hydroxybutyryl, 3-hydroxybutyryl and hydroxypentanoyl; examples of **C_{1-6}alkoxyC_{1-6}alkylcarbonyl** include methoxyacetyl, methoxypropionyl, ethoxybutyryl and butoxyacetyl; examples of **phenylC_{1-6}alkyl** include benzyl, phenylethyl and phenylpropyl; examples of **-CO-C_{1-4}alkyl-Ph** include phenylacetyl and phenylpropionyl; examples of **-CO-C_{1-4}alkyl-heteroaryl** include 2-(3-pyridyl)-acetyl and 2-(3-thienyl)-acetyl; examples of **N-(C_{1-6}alkyl)carbamoyl** include N-methyl-carbamoyl and N-ethyl-carbamoyl; examples of **N-(diC_{1-6}alkyl)carbamoyl** include N,N-dimethylcarbamoyl and N-methyl-N-ethylcarbamoyl.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Second paragraph on page 9, line 7 to page 9, line 20 as follows:

Preferably R^1 is selected from H; -CO-O-$(CH_2)_n$Ph optionally substituted on phenyl hereinabove defined; -CO-O-C_{2-4}alkenyl; -CO-C_{1-4}alkyl; -C_{1-4}alkylene-$CONR^4R^5$ where R^4 and R^5 are independently selected from H, C_{1-4}alkyl.

Most preferably R^1 is hydrogen.

Preferably R^2 is selected from H and -CO-C_{1-4}alkyl.

Most preferably R^2 is hydrogen.

Preferably [L]G is selected from -CH_2-NR^{16}- and -CH_2NR^{16}-T .

Preferably A is selected from phenyl, naphthyl, pyridyl and thienyl.

Most preferably A is phenyl or naphthyl.

Preferably combinations of R^3 and p are selected from:

i) R^3 is selected from a group of Formula II, -C_{1-4}alkylR^7, -O-R^7 and R^7; and p=1-3 with the proviso that at least one of R^3 is a group of the Formula II;

ii) p=0 with the proviso that A is naphthyl and [L]G is -CH_2NR^{16}-T; and

iii) p=1 with the proviso that R^3 = a group of Formula II and A is phenyl or naphthyl.

First paragraph on page 10 line 4 to page 10, line 15 as follows:

Suitable values for [L]G= $CHNR^{16}$ T include CH_2.N(CO.CH_2.$CHMe_2$).CH_2.CH_2; CH_2.N(CH_2 CH_2 CH_2OMe).CH_2.CH_2; CH_2.N(CH_2.pPh.OMe).CH_2.CH_2; CH_2.N(CO.CH_2.$CHMe_2$).CH_2; CH_2N(CO.CH_2.CH_2.CH_2.Me).CH_2; CH_2N(CO.CH_2.CHMe.CH_2Me).CH_2; CH_2N(CO.CH_2.CH_2.OMe)CH_2; CH_2N(CO.CH_2.pyridin-3-yl).CH_2; CH_2N(4-methoxybenzyl)CH_2; CH_2N(CO.CH_2.$CHMe_2$)CH_2.CH_2.CH(Ph); CH_2N(CO.CH_3)CH_2.CH_2.CH(Ph); CH_2N(CO.CH_2.$CHMe_2$)CH_2; CH_2N(CO.CH_3)CH_2; CH_2N(CO.CH_2.$CHMe_2$)CH_2.CH(Ph);

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

$CH_2N(CO.CH_2.CMe_3)CH_2.CH(Ph)$; $CH_2N(CO.CH_2$.pyridin-3-yl$)CH_2.CH(Ph)$; CH_2N(CO.1-hydroxy-6-methoxy-pyridin-3-yl$)CH_2.CH(Ph)$; CH_2N $(CO.CH_2$ pyrid-3-yl$)CH_2CH(Ph)$; $CH_2N(CO.CH_2CHMe_2)CH_2.CH_2$; $CH_2N(CO.CH_2CMe_3)CH_2.CH_2$; CH_2N(CO thiazol-2-yl$)CH_2CH_2$; CH_2N (CO 1-oxido-6-hydroxypyridin-3-yl$)CH_2CH_2$; $CH_2N(CO.CH_2$pyridin-3-yl$)CH_2.CH_2$ and CH_2N(CO.4-methoxybenzyl$)CH_2.CH_2$.

Third paragraph on page 10, line 20 to page 10, line 22 as follows:

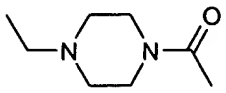
Suitable values for [L]G = $-CH_2NR^{16}-$ include CH_2NH; CH_2NMe; $CH_2N(CO.CH_2.CHMe_2)$ and $CH_2N(CO.CH_2.CH_2.OMe)$. A preferred value for $-CH_2NR^{16}-$ is $-CH_2NH_2-$.

Fourth paragraph on page 10, line 23 to page 10, line 26 as follows:

When [L]G is -CH_2NR16-T- a suitable value for m is 1. When [L]G is $-CH_2-NR^{16}$-CO-T^1- a suitable value for m^1 is 1. When [L]G is $-CH_2-NR^{16}$-T- a suitable value for m is 1. When [L]G is [-CH2-S-T-]-CH_2-S-T- a suitable value for m is 1. When [L]G is $-CH_2$-O-T- a suitable value for m is 1. [L]G is especially -CONH-, $-CH_2$-NH-, $-CH_2NHSO_2-$, $-CH_2NHCO-$.

Fifth paragraph on page 10, line 27 to page 11, line 5 as follows:

In another aspect [L]G is of the formula

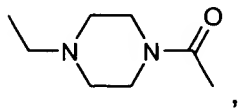


wherein the piperazine ring is optionally substituted by C_{1-4}alkoxyC_{1-4}alkyl, phenoxyC_{1-4}alkyl or heteroaryloxyC_{1-4}alkyl.

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

First paragraph on page 11, line 1 to page 11, line 5, as follows:

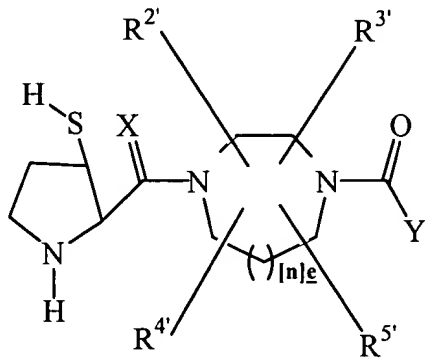
Preferably, when [L]G is of the formula



A is naphthyl.

First paragraph on page 19, line 20 to page 21, line 21 as follows:

In another aspect of the present invention there is provided a compound which inhibits farnesyl-protein transferase of the formula [A]B:



[A] B

wherein:

X is O or H_2;

e[n] is 0 or 1;

t is 1 to 4;

$R^{2'}$, $R^{3'}$, $R^{4'}$, and $R^{5'}$ are independently selected from: H; C_{1-8}alkyl, alkenyl, alkynyl, aryl, heterocycle, -CO-$NR^{6'}R^{7'}$ or -CO-$OR^{6'}$, unsubstituted or substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:

   a. C_{1-4}alkyl,

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

b. $(CH_2)_tOR^{6'}$,

c. $(CH_2)_tNR^{6'}R^{7'}$,

d. halogen,

2) C_{3-6}cycloalkyl,

3) $OR^{6'}$,

4) $SR^{6'}$, $S(O)R^{6'}$, $SO_2R^{6'}$,

5) $-NR^{6'}R^{7'}$,

6) $-NR^{6'}-CO-R^{7'}$,

7) $-NR^{6'}-CO-NR^{7'}R^{8'}$,

8) $-O-CO-NR^{6'}R^{7'}$,

9) $-O-CO-OR^{6'}$,

10) $-O-NR^{6'}R^{7'}$,

11) $-SO_2NR^{6'}R^{7'}$,

12) $-NR^{6'}-SO_2-R^{7'}$,

13) $-CO-R^{6'}$, or

14) $-CO-OR^{6'}$;

and any two of $R^{2'}$, $R^{3'}$, $R^{4'}$, and $R^{5'}$ are optionally attached to the same carbon atom;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

1) C_{1-4}alkyl, unsubstituted or substituted with:

a. C_{1-4}alkoxy,

b. $NR^{6'}R^{7'}$,

c. C_{3-6}cycloalkyl,

d. aryl or heterocycle,

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

e. HO,

2) aryl or heterocycle,

3) halogen,

4) $OR^{6'}$,

5) $NR^{6'}R^{7'}$,

6) CN

7) NO_2, or

8) CF_3;

$R^{6'}$, $R^{7'}$ and $R^{8'}$ are independently selected from: H; C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4}alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e) $-CO-R^{9'}$,

f) $-SO_2R^{9'}$, or

g) NRR^1, wherein

$R^{6'}$ and $R^{7'}$ may be joined in a ring, and

$R^{7'}$ and $R^{8'}$ may be joined in a ring;

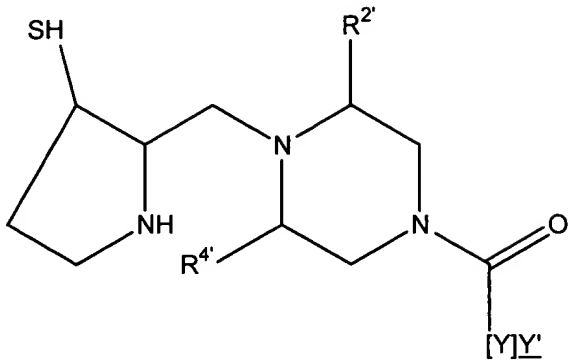
$R^{9'}$ is C_{1-4}alkyl or aralkyl;

or a optical isomer, disulfide or pharmaceutically acceptable salt thereof.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

First paragraph on page 21, line 22 to page 22, line 2 as follows:

A preferred subclass of the formula [A]B is:



wherein $R^{2'}$ and $R^{4'}$ are independently hydrogen and [Y]Y' is C_{1-4}alkyl, phenyl or a 5 or 6 membered heteroaryl ring containing up to 3 heteroatoms selected from N, O and S or of the formula -C_{1-4}alkyl $OR^{10'}$ wherein $R^{10'}$ is C_{1-4}alkyl, phenyl or 5 or 6-membered heteroaryl containing up to 3 heteroatoms selected from N, O and S. Preferably $R^{10'}$ is C_{1-4}alkyl.

First paragraph on page 22, line 3 as follows:

Preferably [Y]Y' is naphthyl.

Second paragraph on page 22, line 4 to page 22, line 18 as follows:

The aspect of the invention relating to Formula [A]B involves compounds related to those disclosed PCT patent application WO 95/00497 (Graham et al.); see the complete specification and claim 1 in particular. Formula [A]B above is based on Formula A in WO 95/00497 (Graham et al.) but with the 3-sulfanylpyrrolidine moiety of the present invention replacing the cysteine-like moiety on the left hand side of Formula A in WO 95/00497 (Graham et al.). Optionally the nitrogen and/or thiol atoms in the pyrrolidine moiety of Formula [A]B may be substituted by taking the values for R^1 and R^2

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

in Formula I as set out herein. Compounds within the scope of Formula [A]B may be prepared by a skilled person using the synthetic details in WO 95/00497 (Graham et al.) combined with the present specification. Preferred compounds for this aspect of the invention correspond to those set out in claims 6-12 of WO 95/00497 (Graham et al.) but with the 3-sulfanylpyrrolidin-2-yl-methyl moiety of the present invention replacing the $HS-CH_2-CH(NH_2)-CH-$ moiety on the left hand side of the relevant compounds attached to the piperazine ring as drawn out in the claims. A preferred compound is (2S)-2-(2-methoxy-ethyl)-1-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine; see Example 7 herein.

First paragraph on page 32, line 4 to page 32, line 24, as follows:

Compounds of Formula I in which [L]G represents $-CO-NR^{16}-$ may be prepared by forming an amide bond between compounds 1 and 2 as outlined in Scheme 1. Compounds of Formula I in which [L]G represents $-CO-NR^{16}-T-$ may be prepared by an analogous procedure. Suitable coupling conditions include the following.

i) Use of EEDQ at ambient temperature in an organic solvent (e.g. dichloromethane, methanol).

ii) Use of oxalyl chloride in an organic solvent (e.g. CH_2Cl_2), DMF in a catalytic amount, in the presence of an organic base (e.g. NMM, triethylamine, DMAP) at 0° C to ambient temperature for 0.5-16h.

iii) Use of EDC/HOBT in an organic solvent (e.g. DMF, CH_2Cl_2).

iv) Use of DCCI/HOBT in an organic solvent (e.g. DMF, CH_2Cl_2) in the presence of an organic base (e.g. triethylamine).

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

v) Use of mixed anhydride reactions under standard conditions, for example isopropylchloroformate in an organic solvent (e.g. DMF, DMA, dichloromethane) in the presence of an organic base (e.g. NMM, DMAP, triethylamine).

vi) Via an active ester under standard conditions e.g. pentafluorophenyl ester in an organic solvent (e.g. dichloromethane) in the presence of an organic base (e.g. triethylamine).

vii) Via an acid chloride under standard conditions e.g. thionyl chloride and heat for about 150min followed by an organic base (e.g. triethylamine) in the presence of an organic solvent (e.g. acetonitrile).

Second paragraph on page 32, line 24 to page 33, line 3, as follows:

Compounds of Formula I in which [L]G represents $-CH_2NR^{16}-$, $-CH_2O-$ or $-CH_2S-$ may be prepared as outlined in Scheme 2. LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents S, O or NR^{16}. Suitable coupling conditions include the following.

i) Use of an inorganic base (e.g. $NaHCO_3$, NaH, K_2CO_3, butyllithium) in an organic solvent (e.g. THF, DMF, DMSO) and a tempterature of about 65° to 150° C

ii) Uses of an organic base (e.g. triethylamine, DMAP) in an organic solvent (e.g. THF, dichloromethane, DMA, DMF) at a temperature range of room temperature - 150° C

iii) Use of an inorganic base (e.g. KOH, NaOH, K_2CO_3) in an aqueous (e.g. water) and organic solvents (e.g. dichloromethane) in a 2 phase system, optionally in the presence of a phase transfer catalyst (e.g. tetrabutylammoniumbromide).

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

First paragraph on page 33, line 4 to page 33, line 12, as follows:

Compounds of Formula I in which [L]G represents -CH=CR^{16}- may be prepared using a Wittig reaction as outlined in Scheme 3. Suitable reaction conditions include the following.

i) Use of a base (e.g. potassium carbonate, metal hydride, metal alkoxide) in the presence of an organic solvent (e.g. THF, toluene, DMSO) optionally in the presence of an aqueous solvent (2-phase system) and optionally in the presence of a catalyst complexing agent which solubilises alkali metal ions in the non-polar solvents such as 1,4,7,10,13-pentaoxacylopentadecane (also called 15-Crown-5) or 1,4,7,10,13,16-hexaoxacyclooctadecane (also called 18-Crown-6).

Second paragraph on page 33, line 13 to page 33, line 18, as follows:

Compounds of Formula I in which [L]G represents -CH_2-NR^{16}- may be prepared as outlined in Scheme 4 by coupling aldehyde (2) with compound 4. Suitable coupling conditions include the following.

i) Use of reducing agent (e.g. $NaCNBH_3$, hydrogen plus catalyst, $LiHBEt_3$, di-isobutyl-aluminiumhydride, lithium aluminium hydride, sodium borohydride) in the presence of a suitable solvent e.g. ethanol and acetic acid.

Fifth paragraph on page 33, line 28 to page 34, line 2, as follows:

Compounds of Formula I in which [L]G represents -CH_2-NR^{16}-T-, -CH_2-O-T- or -CH_2-S-T- may be prepared as outlined in Scheme 5 in which LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents O, S or NR^{16}. Suitable

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

coupling conditions are as outlined above in relation to Scheme 2. Optionally the positions of LG and XH in compounds 1 [&]and 2 in Scheme 5 can be reversed to give the same end product.

First paragraph on page 34, line 3 to page 34, line 10, as follows:

Compounds of Formula I in which [L]G represents $-CH_2-NR^{16}-SO_2-$ may be prepared as outlined in Scheme 6. Compounds 1 [&]and 2 may be coupled under standard conditions such as the following.

i) Use of an organic base (e.g. di-isopropyl-ethylamine, triethylamine, 4-methyl-morpholine) in the presence of an organic solvent (e.g. dichloromethane(at a temperature range of 0°-40° C

ii) Use of an inorganic base (e.g. potassium carbonate) in the presence of an organic solvent (e.g. DMF) at a temperature range of 0°-150°

Second paragraph on page 34, line 11 to page 34, line 13, as follows:

Compounds of Formula I in which [L]G represents $-CH_2-NR^{16}-CO-T-$ may be prepared as outlined in Scheme 7. Compounds 1 [&]and 2 may be coupled under standard conditions such as described above for G = $-CO-NR^{16}-$.

Fifth paragraph on page 34, line 14 to page 34, line 18, as follows:

Compounds of Formula I in which [L]G represents $-CH_2-CHR^{16}-$ may be prepared by reduction of compounds of the type set out as compound 3 in Scheme 3. Reduction is carried out under standard conditions with standard reagents for example using

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

hydrogenation in the presence of a catalyst such as palladium on charcoal at ambient temperature.

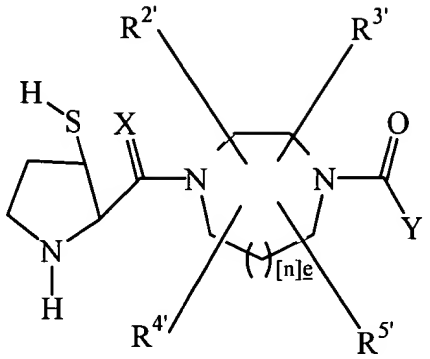
Sixth paragraph on page 34, line 19 to page 34, line 23, as follows:

Compounds of the formula I in which [L]G represents $-CH_2NR^{16}-$, $-CONR^{16}$, $CH_2N(R^{16})$-T- or $-CH_2N(R^{16})COT-$ wherein R^{16} is not hydrogen, may be prepared from the appropriate compound of the formula I wherein R^{16} is hydrogen by introducing the appropriate R^{16} by acylation, alkylation etc. For example, by using similar methods to those disclosed in the specific examples.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Amendments to the Claims

7. A compound of the formula [A]B:



[A] B

wherein:

X is O or H_2;

[n] e is 0 [or 1];

t is 1 to 4;

$R^{2'}$, $R^{3'}$, $R^{4'}$, and $R^{5'}$ are independently selected from: H; C_{1-8}alkyl, alkenyl, alkynyl, aryl, heterocycle, -CO-$NR^{6'}R^{7'}$ or -CO-$OR^{6'}$, unsubstituted or substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:

   a. C_{1-4}alkyl,

   b. $(CH_2)tOR^{6'}$,

   c. $(CH_2)tNR^{6'}R^{7'}$,

   d. halogen,

2) C_{3-6}cycloalkyl,

3) $OR^{6'}$,

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

4) $SR^{6'}$, $S(O)R^{6'}$, $SO_2R^{6'}$,

5) $-NR^{6'}R^{7'}$,

6) $-NR^{6'}-CO-R^{7'}$,

7) $-NR^{6'}-CO-NR^{7'}R^{8'}$,

8) $-O-CO-NR^{6'}R^{7'}$,

9) $-O-CO-OR^{6'}$,

10) $-O-NR^{6'}R^{7'}$,

11) $-SO_2NR^{6'}R^{7'}$,

12) $-NR^{6'}-SO_2-R^{7'}$,

13) $-CO-R^{6'}$, or

14) $-CO-OR^{6'}$;

and any two of $R^{2'}$, $R^{3'}$, $R^{4'}$, and $R^{5'}$ are optionally attached to the same carbon atom;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

1) C_{1-4}alkyl, unsubstituted or substituted with:

   a. C_{1-4}alkoxy,

   b. $NR^{6'}R^{7'}$,

   c. C_{3-6}cycloalkyl,

   d. aryl or heterocycle,

   e. HO,

2) aryl or heterocycle,

3) halogen,

4) $OR^{6'}$,

5) $NR^{6'}R^{7'}$,

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

6) CN

7) NO_2, or

8) CF_3;

$R^{6'}$, $R^{7'}$ and $R^{8'}$ are independently selected from: H; C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4}alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e) $-CO-R^{9'}$,

f) $-SO_2R^{9'}$, wherein

$R^{6'}$ and $R^{7'}$ may be joined in a ring, and

$R^{7'}$ and $R^{8'}$ may be joined in a ring;

$R^{9'}$ is C_{1-4}alkyl or aralkyl;

a pharmaceutically acceptable salt thereof.

8. The [A] compound [according to claim 1 which is any one of the following individual compounds or a pharmaceutically acceptable salt thereof:
(2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester ;
(2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid ;
(2S)-2-({2-phenyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;
(2S)-2-({2-phenyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

(2S)-2-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl)amino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester ;

(2S)-2-({3-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl)amino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid ;

(2S)-2-({-3-phenyl-5[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;

(2S)-2-({-3-phenyl-5[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;

(cis)-2-[{N-(4-methoxybenzyl)- N-(naphthalen-1-ylmethylamino}-methyl]-pyrrolidine-3-thiol ;

N-(naphthalen-1-ylmethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl)-pentanamide;

N-(naphthalen-1-ylmethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl)-2-(pyridin-3-yl)-acetamide ;

N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide ;

N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-acetamide ;

(cis)-2-{[(3-methoxypropyl)-(2-naphthalen-1-ylethyl)amino]methyl}- pyrrolidine-3-thiol;

N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide;

(cis)-2-{[(2-(4-methoxyphenyl)ethyl)-(2-naphthalen-1-ylethyl)amino] methyl}- pyrrolidine-3-thiol;

N-(2,2-diphenyl-ethyl)-N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-butyramide ;

N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-butyramide;

N-(2,2-diphenyl-ethyl)-N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-butyramide;

(2S)-2-{3-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-(3-methoxy-propyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid ;

N-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-butyramide;

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

(2S)-4-carbamoyl-2-({2-phenyl-5-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butyric acid;

(2S)-4-carbamoyl-2-({2-phenyl-5-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butyric acid methyl ester;

2-(3-pyridyl)-N-(2,2-diphenyl-ethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl)- acetamide;

6-methoxy-1-oxido-N-(2,2-diphenyl-ethyl)-N-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-pyridine-3-carboxamide;

N-(naphthyl-1-yl-ethyl)-N-[(cis)-3-sulfanylpyrrolidin-2yl-methyl)-thiazole-5-carboxamide;

6-methoxy-1-oxido-N-(naphthyl-1-yl-ethyl)-N-[cis)-3-sulfanylpyrrolidin-2-ylmethyl]-pyridine-3-carboxamide;

(2S)-2-{2-benzyl-4-[(cis)-3-sulfanyl-pyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanyl-butyric acid;

(2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl)amino]-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{2-benzyl-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl)amino]-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{2-phenethyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylaminobenzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{phenethyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{2-benzyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{2-(phenethyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{2-(4-methylphenylethynyl)-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid;

(2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid isopropyl ester;

(2S)-2-{2-benzyl-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

(2S)-2-{2-benzyl-4-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
(2S)-2-{2-benzyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
(2S)-2-{2-phenyl-5-[(trans)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
(2S)-2-{2-phenyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
(2S)-2-{2-benzyl-5-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
(2S)-2-{2-(4-methylphenethyl)-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
(2S)-2-{2-(4-methylphenylethynyl)-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester;
(2S)-2-(2-methoxyethyl)-1-[(cis)-3-sulfanylpyrrolidin-2-ylmethyl]-4-(naphth-1-oyl)piperazine;
(cis)-2-[N-isovaleryl-N-(2-(napth-1-yl)ethyl)aminiomethyl]-3-sulfanylpyrrolidine;
(cis)-2-[N-(3-pyridylacetyl)-N-(naphth-1-yl)ethyl)aminomethyl]-3-sulfanylpyrrolidine;
(cis)-2-[N-1-oxido-6-methoxypyridin-3-ylcarbonyl) -N-(naphth-1-yl)ethyl)aminomethyl]-3-sulfanylpyrrolidine;
(cis)-2-[N-thiazol-5-ylcarbonyl) -N-(naphth-1-yl)ethyl)aminomethyl]-3-sulfanylpyrrolidine;
(2S)-2-[2-(4-fluorophenethyl)-4-[(cis)-3-sulfanyl)-pyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyric acid;
methyl (2S)-2-[2-(4-fluorophenethyl)-4-[(cis)-3-sulfanylpyrrolidin-2-ylmethylamino)benzoylamino]-4-methylsulfanylbutyrate;
(2S)-2-[2-(4-fluorophenethyl)-4-((2R,3R)-3-sulfanyl-pyrrolidin-2-ylmethylamino)benzoylamino]-5-methylsulfanylbutyric acid;
(2S)-2-{2-Benzyl-5-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid methyl ester ;
(2S)-2-{2-Benzyl-5-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanylbutyric acid ;

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

(2S)-2-({2-phenyl-5-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;

(2S)-2-({2-phenyl-5-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;

(2S)-2-({3-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester ;

(2S)-2-({3-[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-naphthalene-1-carbonyl}-amino)-4-methylsulfanylbutyric acid ;

(2S)-2-({-3-phenyl-5[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid methyl ester;

(2S)-2-({-3-phenyl-5[([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-4-methylsulfanylbutyric acid;

(2R,3R)-2-[{N-(4-methoxybenzyl)- N-(naphthalen-1-ylmethyl)-amino}-methyl]-pyrrolidine-3-thiol ;

N-(naphthalen-1-ylmethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-pentanamide;

N-(naphthalen-1-ylmethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2-ylmethyl)-2-(pyridin-3-yl)-acetamide;

N-((2R,3R)-3-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-N-(2-naphthalen-1-yl-ethyl)butyramide;

N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-N-(2-naphthalen-1-yl-ethyl)-2-pyridin-3-yl-acetamide;

(2R,3R)-2-{[(3-Methoxypropyl)-(2-naphthalen-1-ylethyl)amino]methyl}- pyrrolidine-3-thiol;

N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-2-(4-methoxy-phenyl)-N-(2-naphthalen-2-yl-ethyl)-acetamide;

(2R,3R)-2-{[(2-(4-Methoxyphenyl)ethyl)-(2-naphthalen-1-ylethyl)amino] methyl}-pyrrolidine-3-thiol;

N-(2,2-Diphenyl-ethyl)-N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3-methyl-butyramide;

N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-2-yl-ethyl)-butyramide;

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

N-(2,2-Diphenyl-ethyl)-N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-butyramide;

(2S)-2-{3-[([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-(3-methoxy-propyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid ;

N-([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-3,3-dimethyl-N-(2-naphthalen-1-yl-ethyl)-butyramide;

(2S)-4-carbamoyl-2-({2-phenyl-5-[([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butyric acid;

(2S)-4-carbamoyl-2-({2-phenyl-5-[([2R,3R]-3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-phenylcarbonyl}-amino)-butyric acid methyl ester;

2-(3-pyridyl)-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)-acetamide;

6-methoxy-1-oxido-N-(2,2-diphenyl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)-pyridine-3-carboxamide;

N-(naphthyl-1-yl-ethyl)-N-([2R,3R]-3-sulfanylpyrrolidin-2yl-methyl)-thiazole-5-carboxamide;

6-methoxy-1-oxido-N-(naphthyl-1-yl-ethyl)-N-((2R,3R)-3-sulfanylpyrrolidin-2-ylmethyl)-pyridine-3-carboxamide;

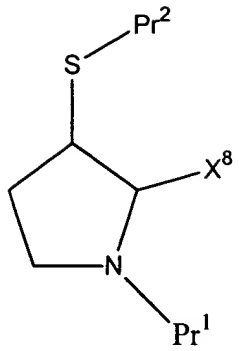
(2S)-2-{2-benzyl-4-[([2R,3R]3-sulfanyl-pyrrolidin-2-ylmethyl)-amino]-benzoylamino}-4-methylsulfanyl-butyric acid; and]

(2S)-2-(2-methoxy[-]ethyl)-1-((cis)[[2R,3R]]-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition which comprises a compound according to any one of claims [1, 3] 7[,] or 8 and a pharmaceutically acceptable carrier.

13. A process for preparing compounds of the Formula [I]B as defined in claim [1]7 which comprises deprotecting a compound of Formula VI:

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000



wherein X^8 represents the right hand side of the Formula [I]B as defined in claim [1]Z, Pr^1 is H or an amino protecting group, Pr^2 is H or a thio protecting group and any functional groups in X^8 are optionally protected with the proviso that there is at least one protecting group and optionally, if desired, converting the product thus obtained into a pharmaceutically acceptable salt thereof.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000